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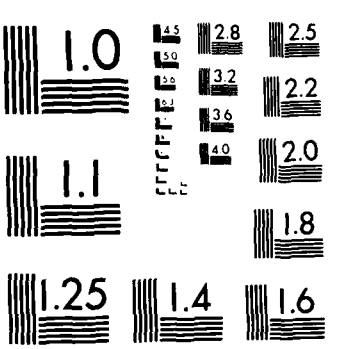

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This study examined the effectiveness of Spironolactone as a prophylactic agent for the prevention of Acute Mountain Sickness (AMS). Spironolactone 25mg PO QID or placebo was administered to 9 subjects in a double-blind placebo controlled cross over design. Medication was given for 48h prior to and during a 46 h exposure to 427 torr (4570m) in a hypobaric chamber. Six subjects demonstrated prevention of either the cerebral or respiratory symptoms of AMS during at least 1 segment of the altitude sojourn.

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EFFECT OF SPIRONOLACTONE ON ACUTE MOUNTAIN SICKNESS

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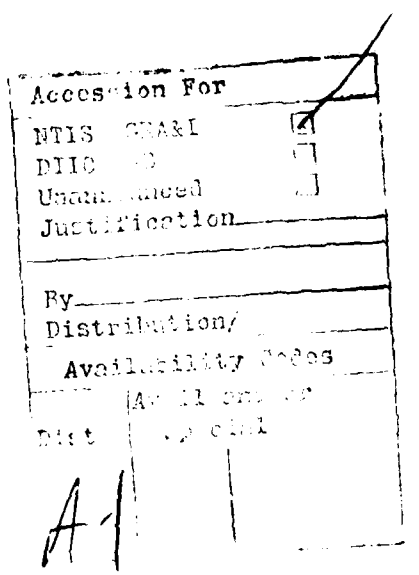

EFFECT OF SPIRONOLACTONE ON ACUTE MOUNTAIN SICKNESS

Acute mountain sickness (AMS) is a multisystem disorder principally characterized by headache, impaired sleep, lassitude, nausea, vomiting and shortness of breath. Symptoms appear within 24 hours after abrupt arrival of the unacclimatized lowlander to terrestrial elevations above 3000m. Individual susceptibility varies, however rapid ascent to altitudes in excess of 4000m will produce significant impairment in a majority of persons. The syndrome is self-limited and usually resolves within 3 to 4 days of continuous exposure (1-3).

Prophylactic measures known to reduce the severity and frequency of AMS include administration of acetazolamide (4) dexamethasone (5), and/or gradual ascent over several days incorporating frequent rest periods (6). Limitations of these measures including incomplete effectiveness, risk of medication-induced side effects and time constraints have prompted search for additional remedies. Several anecdotal (7,8), non-controlled (9), and controlled reports (10,11) have suggested that the aldosterone antagonist spironolactone may be an effective prophylactic agent for AMS. These reports were based on data obtained during trekking expeditions where variables other than hypoxia may have influenced results. This report describes the evaluation of spironolactone as a prophylactic agent for AMS using a double-blind placebo-controlled crossover design in a hypobaric chamber at a simulated elevation of 4570m.

METHODS

Twelve male volunteers, ages 19-25, served as test subjects after giving their informed consent. All were native lowlanders and had not been

SUMMARY

This study examined the effectiveness of Spironolactone as a prophylactic agent for the prevention of Acute Mountain Sickness (AMS). Spironolactone 25mg PO QID or placebo was administered to 9 subjects in a double-blind placebo controlled cross over design. Medication was given for 48h prior to and during a 46h exposure to 427 torr (4570m) in a hypobaric chamber. Six subjects demonstrated prevention of either the cerebral or respiratory symptoms of AMS during at least 1 segment of the altitude sojourn.

exposed to high altitude during the 6 months prior to the study. All twelve subjects participated in the first altitude exposure period and nine subjects completed the crossover phase. One subject was excluded from the crossover phase due to a viral syndrome. Another was withdrawn after 12 hours of altitude exposure because of unexplained chest pain which resolved without sequellae after removal from the hypobaric chamber. An additional subject voluntarily withdrew from participation for personal reasons prior to the crossover phase. Only data from nine subjects were analyzed.

STUDY DESIGN

The study employed a double-blind placebo-controlled crossover design. Treatment order was randomized between subjects and balanced between trials. Treatment consisted of administration of either 25mg spironolactone or a physically indistinguishable placebo orally four times per day for 48h prior to ascent and during 46h of simulated altitude exposure.

For 48 hours prior to ascent the subjects were confined to a dormitory for sea-level testing (Natick, MA 50m). During sea-level confinement and subsequent altitude exposures they received a diet consisting of US Army operational rations of known elemental composition three times daily and water ad lib. All intake of food and water was weighed and recorded. At 1800h on the second day of confinement, subjects entered a hypobaric chamber which was then evacuated over a 10-minute period to a barometric pressure of 427 torr, equivalent to an altitude of 4570 m. Subjects remained in the hypobaric chamber for 46h and were sedentary during the period of confinement. Two weeks after the initial hypobaric exposure, the subjects crossed over to the alternate therapy and the protocol was repeated.

ASSESSMENT OF SYMPTOMS

Symptoms of AMS were evaluated using the Environmental Symptoms Questionnaire which was administered to the subjects twice daily during the 48h period of sea-level confinement and the 46h period of hypobaric exposure using an interactive computer software package. This 67-question symptom inventory has been used to quantitate symptom severity under stressful environmental conditions (12). Intensity of symptoms was expressed using six identifiers ranging from "not at all" through "slight," "somewhat," "moderate," "quite a bit" and "extreme." Each identifier was employed in a declarative sentence. All six sentences appeared on the computer screen simultaneously. The subject selected one of the six sentences which most closely described his feeling at that time, such as "I do not feel dizzy" or "I feel extremely dizzy." The computer was programed to check the consistency of responses and to assign a numerical value from zero (not at all) to five (extreme) for each of the 67 responses. To assess the degree of acute mountain sickness, a weighted average of cerebral symptoms labeled "AMS-C" and a weighted average of respiratory symptoms labeled "AMS-R," was derived from the score. The leading components of AMS-C were "feel sick," "feel hungover," "coordination off," "dim vision," "lightheaded," and "headache." AMS-R incorporated such responses as "hard to breathe," "short of breath," "hurts to breathe." Previous studies have validated that these measures of acute mountain sickness accurately and reliably identify individuals who are "sick" under hypobaric conditions (13).

BIOCHEMICAL AND PHYSIOLOGICAL MEASUREMENTS

Daily determinations at sea level and altitude were performed of each of

the following: water, caloric, sodium and potassium consumption; urine volume and urinary sodium, potassium and creatinine excretion. Fasting morning venous blood was obtained daily for measurement of hematocrit, hemoglobin, electrolytes, urea nitrogen and glucose. Arterial blood samples were obtained once at sea level prior to medication administration and once during each altitude exposure for analysis of pH, PaO_2, and $PaCO_2$. Sitting and supine blood pressures were measured daily, as were resting minute ventilation and oxygen consumption. These determinations were performed at the same time of day for each subject.

PSYCHOLOGICAL ASSESSMENT

Prior to altitude exposure, the subjects completed the Body Consciousness Questionnaire. This is a 15 item self-report instrument used to determine the degree to which people attend to their internal sensations. In previous studies, subjects who scored high on the private body consciousness scale, a score derived from the Questionnaire, were more aware of the physiological changes induced by caffeine ingestion than those who scored lower on the scale (14).

STATISTICAL ANALYSIS

Data are represented as means ± S.E. The Wilcoxon matched-pairs-signed ranks test was used to compare paired ESQ symptom score differences between spironolactone and placebo treatments. Physiological and biochemical parameters were compared using appropriately paired or non-paired two-tailed t-tests.

RESULTS

No subject experienced the symptoms of AMS during sea-level confinement while on spironolactone or placebo. Spironolactone prevented the symptoms of AMS in six subjects when compared against placebo. These subjects were "well" on the agent and "sick" off for either AMS-C, AMS-R or both on one or more occasion during the period of simulated hypobaric hypoxia. None of this group labeled "responders" exhibited any adverse reactions or increase of symptoms while on the active agent.

Three subjects experienced at least one episode of worsening of symptoms when on spironolactone. Two of those had at least one ESQ score which demonstrated increased symptoms of AMS-C while on spironolactone and two also demonstrated worsening of AMS-R during one period while on the agent. Two of the three subjects in this category also had at least one episode of improvement in AMS-C or AMS-R at some time during the 46h altitude exposure. The three subjects who had worsening of symptoms were labeled "non-responders." The symptom status of individual test subjects are displayed in Table 1.

Of the eight paired comparisons of AMS-C and AMS-R on and off spironolactone statistical significance was noted in one. At the 30th hr of altitude exposure, the symptoms of AMS-R were significantly less while on the active agent ($p = .04$). At the 40th hour of exposure these symptoms again were decreased, however at a lower degree of significance ($p = .10$). The self-limited nature of AMS was evidenced by the increased number of subjects "well" on and off spironolactone during the last 24 hours of altitude exposure. Table 2 lists the number of subjects "sick" or "well" as determined by scores on the Environmental Symptoms Questionnaire during exposure to altitude. Responders were those subjects who were "sick" while on placebo but "well" on spironolactone.

Table 3 presents the values of measured biochemical and physiological variables of responders and non-responders on and off spironolactone. A higher NaCl consumption and elevated BUN was noted in the non-responders. Responders when compared to themselves on and off spironolactone, demonstrated a lower $PaCO_2$ and higher venous hemoglobin while on the active drug.

Responses to the Body Consciousness Questionnaire were very homogeneous. Without exception all subjects had low scores on the Private Body Consciousness Scale. This indicates a similar degree of sensitivity to internal sensations in both responders and non-responders.

DISCUSSION

This study suggests that spironolactone was effective in preventing the symptoms of AMS in some test subjects exposed to simulated altitude in an hypobaric chamber. Although a significant beneficial drug effect was noted in only one of eight-paired comparisons, symptoms of AMS were frequently prevented by prophylactic administration of spironolactone. It is important in studies which employ a small number of subjects not to conclude lack of clinical effectiveness when statistical significance is not achieved (15). Although some statistically significant differences in measured parameters other than symptoms were noted, they do not help explain the basis of the drug effect. For instance, the higher BUN in non-responders on therapy is likely a reflection of the dehydration common in AMS secondary to anorexia, nausea and vomiting. The differences in $PaCO_2$ and hemoglobin concentration are within the errors intrinsic to their measurement.

Of possible note is the higher level of NaCl intake in non-responders. Although this group demonstrated greater salt consumption, there was a high

degree of individual variability. The large variability of intake may have been due to a number of factors including individual taste preference for the processed military combat rations, confinement to a small physical area and a rigidly enforced schedule of meal periods. Both responders and non-responders were fully salt replete prior to ascent, a situation which could not be guaranteed in prior studies evaluating spironolactone.

The results of psychological testing demonstrated that the response or lack of response to spironolactone was not due to differences in sensitivity to body sensations in our test subjects. This control was particularly important since the symptoms of AMS are largely subjective.

The mechanism by which hypobaric hypoxia produces AMS is as yet unknown. Several authors have postulated cerebral edema secondary to hypoxia as the genesis of the symptoms of AMS (1,5). If that is the case, spironolactone may function by preventing hypoxic-induced cerebral edema. Studies using spironolactone in higher doses than used in our study, have shown a reduction in cerebral edema in neurosurgical patients (16), as well as an inhibition of CSF production in an animal model (17). We have no direct evidence that this was the mechanism responsible for the observed prevention of symptoms in our subjects.

In summary, spironolactone has been shown in a double-blind placebo crossover investigation as being a partially effective agent for the prevention of AMS in a group of young sedentary test subjects exposed to simulated hypobaric hypoxia.

TABLE 1

COMPARISON OF SYMPTOMS OF AMS-C AND AMS-R

IN INDIVIDUAL TEST SUBJECTS ON AND OFF SPIRONOLACTONE

	AMS-C				AMS-R				
SUBJECT	HOURS OF EXPOSURE TO 427 TORR								RESPONSE
NUMBER	16	30	40	44	16	30	40	44	
1	I	N	I	N	I	I	I	N	R
2	N	N	W	W	N	N	N	N	NR
3	I	I	N	N	I	I	N	N	R
4	N	I	N	N	N	I	N	N	R
5	N	I	N	N	I	I	N	N	R
6	N	N	N	W	W	N	N	I	NR
7	N	N	N	I	W	N	N	N	NR
8	I	N	N	N	N	N	N	N	R
9	N	N	N	I	N	I	I	I	R

N (NULL) WELL ON/WELL OFF OR
SICK ON/SICK OFF SPIRONOLACTONE

I (IMPROVED) WELL ON/SICK OFF SPIRONOLACTONE

W (WORSENED) SICK ON/WELL OFF SPIRONOLACTONE

R RESPONDER

NR NON-RESPONDER

TABLE 2

Number of Subjects "SICK" or "WELL" as Determined by Scores on the Environmental Symptoms Questionnaire While taking Spironolactone or Placebo

	AMS-C				AMS-R			
	HOURS OF EXPOSURE TO 427 TORR							
	16	30	40	44	16	30	40	44
SICK ON & SICK OFF SPIRONOLACTONE	6	4	2	0	3	1	1	0
WELL ON & WELL OFF SPIRONOLACTONE	0	2	5	5	1	3	6	7
SICK OFF & WELL ON SPIRONOLACTONE (RESPONDERS)	3	3	1	2	3	5	2	2
WELL OFF & SICK ON SPIRONOLACTONE	0	0	1	2	2	0	0	0

TABLE 3

Comparison of Measured Physiological and Biochemical Parameters between "Responders" and "Non-Responders" On and Off Spironolactone

ORAL INTAKE	RESPONDERS ON SPIRONOLACTONE	RESPONDERS OFF SPIRONOLACTONE	NON-RESPONDERS ON SPIRONOLACTONE	NON-RESPONDERS OFF SPIRONOLACTONE
H_2O Intake(ml) Day 2 (SL)	1087 ± 225	1503 ± 451	873 ± 228	1095 ± 404
H_2O Intake(ml) Day 3 (ALT)	736 ± 378	1079 ± 531	864 ± 294	565 ± 459
NaCl Intake(mg) Day 2 (SL)	8080 ± 2016	8908 ± 3208	10874 ± 613	8957 ± 3836
		p = .02		
NaCl Intake(mg) Day 3 (ALT)	1334 ± 1158	p=.01 2372 ± 1243	4873 ± 4087	3787 ± 4405
		p = .05		
K Intake(mg) Day 2 (SL)	2211 ± 881	2477 ± 1147	3075 ± 414	2320 ± 1182
K Intake(mg) Day 3 (ALT)	369 ± 435	606 ± 327	1058 ± 1121	842 ± 421
URINARY OUTPUT				
Urine Vol(ml) Day 2 (SL)	1192 ± 688	1098 ± 480	800 ± 372	843 ± 209
Urine Vol(ml) Day 3 (ALT)	557 ± 458	791 ± 495	430 ± 335	565 ± 459
Urine N_a(Meq/24h) Day 3 (ALT)	99 ± 77	93 ± 62	66 ± 55	79 ± 29
Urine K(Meq/24h) Day 3 (ALT)	26 ± 20	28 ± 19	21 ± 19	31 ± 11

RESPIRATORY MEASUREMENTS

	RESPONDERS ON SPIRONOLACTONE		RESPONDERS OFF SPIRONOLACTONE	NON-RESPONDERS ON SPIRONOLACTONE	NON-RESPONDERS OFF-SPIRONOLACTO
Resting V_{min} (L/min) Day 3 (ALT)	16.3 ± 3.9		15.2 ± 2.8	15.5 ± 2.6	15.8 ± 2.1
Resting V_{o2} (Ml/min) Day 3 (ALT)	322 ± 68		330 ±49	323 ± 56	336 ± 46
Resting PaO_2 (mmHg) Day 3 (ALT)	41.6 ± 1.8		39.2 ± 2.3	41.3 ± 3.5	38.6 ± 2.4
Resting $PaCO_2$ (mmHg) Day 3 (ALT)	22.4 ± 2.0	p=.02	24.0 ± 1.6	23.6 ± 4.0	24.5 ± 2.4
Resting pH(arterial) Day 3 (ALT)	7.49 ± .04		7.49 ± .02	7.49 ± .06	7.48 ± .02

SERUM CHEMISTRY VALUES

Serum Na(Meq/L) Day 3 (ALT)	151.6 ± 11.1		144 ± 8.9	142 ± 3.0	151 ± 9.4
Serum K (Meq/L) Day 3 (ALT)	4.6 ± .3		4.2 ± .4	4.2 ± .4	4.3 ± .4
Serum Cl (Meq/L) Day 3 (ALT)	116.4 ± 8.8		109.8 ± 6.9	109.0 ± 1.9	116.2 ± 7.5
Serum CO_2 (Meq/L) Day 3 (ALT)	20.8 ± 1.1		20.4 ± 1.1	19.3 ± 3.6	20.6 ± 1.5
BUN (Meq/L)	13.6 ± 1.3		14.8 ± 5.6	18.4 ± 2.1	16.4 ± 3.6
			p=.001		

VENOUS HEMOGLOBIN (gm/dL)	16.3 ± .9	p=.02	15.7 ± 1.2	16.0 ± 1.8	15.6 ± 1.1

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